Pleural Fluid Analysis

Maximizing Diagnostic Yield in the Pleural Effusion Evaluation

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Establishing the cause of a pleural effusion can be challenging. Analysis of pleural fluid (PF) is a powerful tool to determine the cause of a pleural effusion. Surprisingly, despite the diagnostic power of PF analysis (PFA), it is often underused. This review provides a practical framework to maximize the diagnostic potential of the PFA. We describe the role of a PFA in establishing the cause of a pleural effusion. We also discuss challenges and limitations of PFA.

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KEY WORDS: exudate; Light's criteria; pleural effusion; pleural fluid analysis; transudate

Case Example

A 29-year-old woman sought treatment at the emergency room with right-sided pleuritic chest pain, dyspnea, night sweats, and nonproductive cough for the previous 2 weeks. She did not report any fever, chills, or weight loss. She was born and raised in Upstate New York. She was a pastor and had carried out missionary work in Mexico and Cambodia 3 years before seeking treatment. Physical examination revealed dullness on percussion and decreased breath sounds at the right hemithorax. Chest radiograph showed a moderate right-sided pleural effusion. Thoracic ultrasound showed an anechoic pleural effusion. Thoracentesis was performed and approximately 1 L of serous fluid was obtained. Pleural fluid analysis (PFA) showed a pleural fluid (PF) total WBC count of 2,708 cells/μL with 83% lymphocytes, PF protein of 4.3 g/dL, PF lactate dehydrogenase (LDH) of 612 U/L, PF pH of 7.38, PF glucose of 59 mg/dL, PF cholesterol of 109 mg/dL with serum protein of 6 g/dL, and serum LDH of 128 U/L. PF gram stain, acid fast bacilli (AFB) stain, and fungal stains showed negative results. Induced sputum did not reveal any AFB.

General Approach to a Pleural Effusion

The general approach to determining the cause of a pleural effusion is outlined in Figure 1. A specific pleural diagnosis rarely is determined based on a PFA alone. A detailed history and physical, radiographic, and sonographic examinations are important tools in determining the cause of a pleural effusion (a description of which is beyond the scope of this article). If the cause of a pleural effusion is obvious based on clinical data and empiric treatment has resulted in favorable resolution of the

ABBREVIATIONS: ADA = adenosine deaminase; CHF = congestive heart failure; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro-brain natriuretic peptide; PEEVO = pleural effusion of extravascular origin; PF = pleural fluid; PFA = pleural fluid analysis

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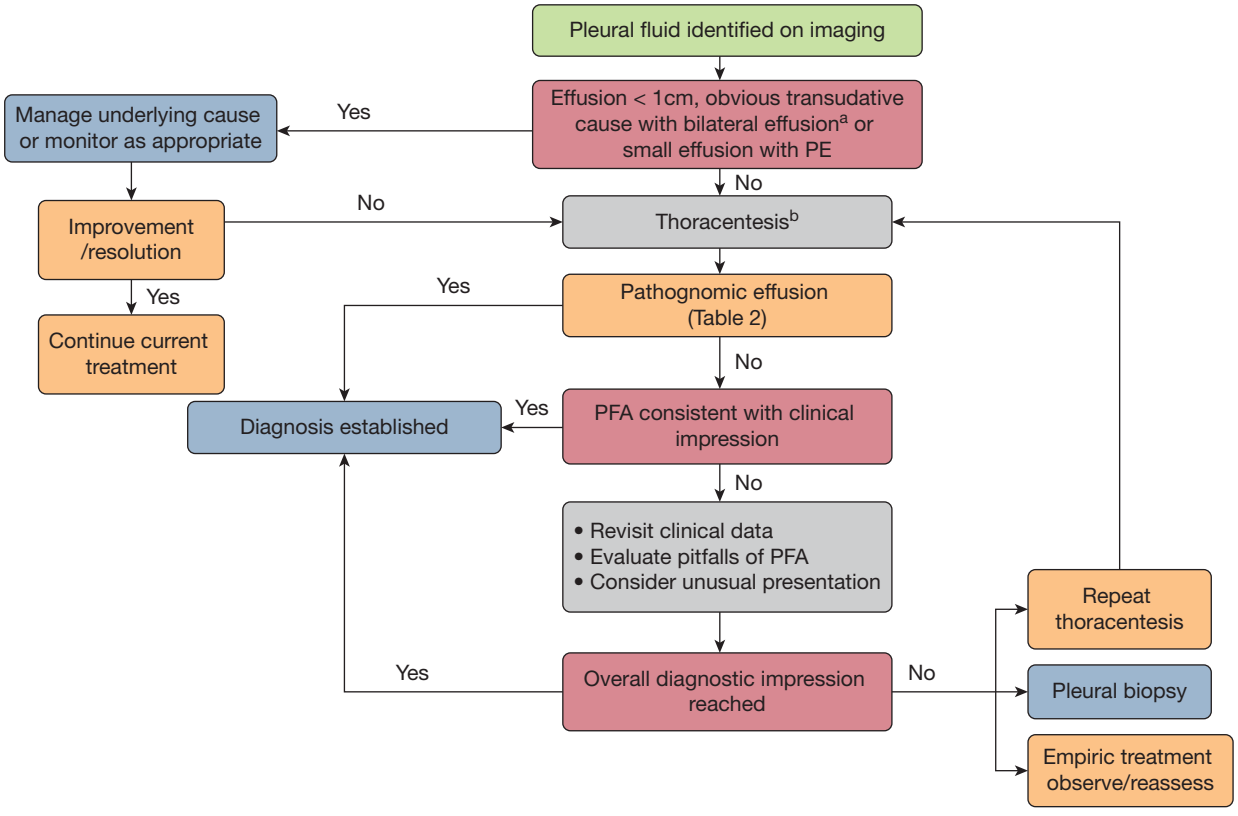

Figure 1 – *Flow diagram showing general approach to the diagnosis of a pleural effusion.* [a]*Obvious transudates: bilateral pleural effusion in patients with congestive heart failure, renal failure, liver failure, or volume overload.* [b]*Thoracic ultrasound can alter the approach; (1) echogenic effusions likely are exudate and need pleural drainage and (2) complex septated and complex homogenous echogenic effusion may need tube thoracostomy and possible intrapleural enzyme treatment. PE = pulmonary embolism; PFA = pleural fluid analysis.*

pleural effusion, then a diagnostic thoracentesis can be avoided. An example of this is a patient who demonstrates worsening exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema, and bilateral pleural effusion, which all respond to diuretics. When PF findings are coupled with an adequate medical history, physical examination, and other laboratory data such as chest imaging and thoracic ultrasonography findings, information may be adequate to secure the cause of a pleural effusion. If the PFA results are not consistent with the impression before thoracentesis, alternative diagnoses and potential pitfalls in PFA interpretation (discussed herein) should be considered. When the diagnosis remains uncertain despite a comprehensive evaluation including PFA, diagnostic options include repeating the thoracentesis, empiric treatment of the likely cause, watchful observation, or pleural biopsy. Although pleural biopsy may be required if malignancy or pleural TB is suspected, it should be noted that pleural biopsies are nondiagnostic in up to 40% of patients.[1]

PF Analysis

PFA is the key component in the evaluation of a pleural effusion. Unfortunately, a detailed analysis of PFA is often neglected by the clinician.[2] Exceptions to performing a thoracentesis for PFA are limited to effusions that are too small to sample safely (< 1 cm in depth on imaging), small ipsilateral effusions associated with pulmonary embolism, or transudates with an obvious clinical cause (eg, decompensated heart failure, decompensated liver failure, end-stage renal failure, or hypoalbuminemia) (Fig 1). In patients with bilateral effusions, PFA from a unilateral thoracentesis usually is sufficient for the diagnostic information, unless a clinical indication exists to suggest differing causes or severities.[3] In general, a thoracentesis should be performed on the larger effusion or on the side of underlying parenchymal infiltrate or mass. Thoracic ultrasonography may aid in the selection of the laterality of the pleural drainage procedure based on the identification of pleural effusion echogenicity or associated abnormal lung parenchyma.

PF Testing

Certain PF studies are routine and almost always should be obtained as part of a PFA (Table 1). These include the components of the Light criteria: PF protein and LDH, alongside corresponding serum levels obtained at the time of thoracentesis.[4,5] PF pH and cell count with differential also are measured routinely because they often assist in establishing the pleural diagnosis (Table 1). To ensure accurate results, the PF pH should be measured within 1 hour of PF collection using a blood gas analyzer. Of note, excessive delay in analysis or the presence of residual air or lidocaine can alter pH results significantly.[6]

For suspected parapneumonic effusions, 10 mL of PF should be inoculated directly into blood culture bottles to improve the microbiological yield.[7] When tuberculous pleural effusion is suspected, the fluid should also be sent for an acid-fast smear and culture. However, pleural cultures for mycobacteria may require 8 weeks to detect the organism, and the yield is low (< 30%).[8] Although nucleic acid testing has a higher diagnostic yield, currently it is not approved for PF testing. In cases of suspected malignancy, 50 to 75 mL of PF is sufficient for the cytologic analysis, because higher volumes do not increase the yield appreciably.[9-12] The detection of malignancy by next generation molecular sequencing testing is based on the proportion of tumor cells to nonnucleated tumor cells in the cell block. Typically, a 20-mL sample with a cell count of around 1,000/mL and an adequate tumor to nontumor nucleated cell ratio (range, 0.2-0.5) is sufficient for the next generation molecular sequencing analysis.[13]

Additional PF testing may be required in selected scenarios (Table 2). PF adenosine deaminase (ADA) levels deserve a special mention because traditionally they are used as a biomarker for the diagnosis of a tuberculous pleural effusion. However, pleural ADA levels can be elevated in several non-TB conditions including malignancy, empyema, and rheumatoid pleural effusion.[14,15] The diagnostic performance of pleural ADA for tuberculous pleural effusion depends on its local prevalence. In nonendemic areas, a pleural ADA of level < 30 IU/L virtually rules out tuberculous pleural effusion with a negative predictive value of 99%.[14,16] However, in endemic areas, no single cutoff can exclude a tuberculous pleural effusion reliably. Nonetheless, a PF ADA level of > 70 IU/L and a lymphocytic predominant pleural effusion in a patient with suspected tuberculous pleural effusion strongly supports the diagnosis.[17,18]

PF Interpretation

When PF is obtained by thoracentesis, gross examination of its color and odor can provide immediate diagnostic clues when coupled with the clinical presentation (Table 3). In select cases, PFA findings may be pathognomonic for specific pleural disorders (Table 4). In the absence of pathognomonic features, the initial step in analyzing the PF should be classifying the effusion as transudative or exudative.[19] This dichotomous classification gives valuable pathophysiologic clues concerning the underlying disease process.[20] Because it is not practical to ascertain mechanistically if a transudative or exudative process has occurred, the Light criteria are used commonly as an imperfect surrogate for this classification.[5,20] It should be noted that this dichotomous transudative-exudative classification does not necessarily define the underlying cause of the pleural effusion; however, this distinction is useful to narrow the differential diagnosis.

The Light criteria use a combination of the ratio of protein and LDH levels in PF and serum as well as the absolute PF LDH value (Table 5).[4] The rationale behind these criteria is that an elevated PF protein reflects increased capillary permeability found with exudates, and an elevated pleural LDH suggests pleural inflammation or high cellular turnover that is also found with exudates.[21] The Light criteria demonstrate a high sensitivity (98%), but lower specificity (72%), for identifying exudates.[22] This emphasis on sensitivity underscores clinical practice considerations because exudates often require specific interventions, such as pleural biopsy for malignancy or targeted treatment for pleural infection, whereas most transudates typically respond to diuresis and management of the underlying organ dysfunction. Although the high sensitivity ensures that exudates are missed rarely, the modest specificity results in the misclassification of almost 30% of transudative effusions as exudates (discussed herein). In addition, up to 10% of malignant pleural effusions can be transudative, especially when an additional competing cause of transudative effusion is present, such as congestive heart failure (CHF), chronic liver disease, or renal disease.[23,24]

The Light criteria have been criticized for rendering dichotomous decisions based on the continuous variables, incorporating 2 statistically correlated

TABLE 1] Differential Causes of Pleural Effusion Based on PFA

Finding	Associated Conditions
Cell count and differential	
Lymphocyte > 80%	Tuberculous pleural effusion
	Sarcoidosis
	Lymphoma[a]
	Chylothorax
	Yellow nail
	Acute lung rejection
	Trapped lung
	Rheumatoid pleural effusion
	After CABG
	Uremic pleural effusion
	Drug induced[b]
Basophils > 10%	Leukemia
Eosinophils > 10%	Hemothorax
	Pneumothorax
	Prior thoracentesis
	Drug induced pleural effusion
	Benign asbestos pleural effusion
	Parasitic infection (paragonimiasis)
	Eosinophilic pneumonia
	Eosinophilic granulomatosis
	Hyper eosinophilic syndrome
	Malignancy
	Bacterial infection
	Fungal infection
	Tuberculous pleural effusion
Mesothelial cells > 5%	Unlikely TB
Nucleated cells > 50,000/μL	Complicated parapneumonic effusion or empyema
	Rheumatoid pleural effusion
	Pancreaticopleural fistula
Nucleated cells 10,000-50,000/μL	Simple parapneumonic effusion
	Lupus pleuritic
	Acute pancreatitis
Biochemistry	
pH < 7.30	Empyema
	Chronic rheumatoid pleural effusion
	Lupus pleuritis
	Esophageal rupture
	Malignancy
	Fungal infection
	Urinothorax[c]
	Normal saline infusion through migrated central line[c]
	Tuberculous pleural effusion
	Paragonimiasis
LDH > 1,000 IU/L	Complicated parapneumonic effusion or empyema
	Rheumatoid pleural effusion
	Body cavity lymphoma
	Paragonimiasis
Protein > 7 g/dL	Multiple myeloma
	Waldenstrom macroglobulinemia
Protein < 1 g/dL	Transudative PF of extravascular origin (PEEVO)
	Hepatic hydrothorax
	Urinothorax
	Peritoneal dialysis-associated pleural effusion
	Extravascular migration of central venous catheter
	Cerebrospinal fluid in pleural space
Glucose < 60 mg/dL[d]	Similar causes as pleural acidosis (pH < 7.30)
Protein discordant (high protein and normal or slightly elevated LDH)	Chylothorax
	Congestive heart failure with diuresis
	End-stage renal disease
	Lung entrapment
	Yellow nail
	Sarcoidosis
	Pleural effusion after CABG
LDH discordant (high LDH and normal or slightly elevated protein)	Viral pleurisy
	Bacterial pneumonia

(Continued)

TABLE 1] *(Continued)*

Finding	Associated Conditions
	Pneumocystis jirovecii pneumonia
	Malignancy

CABG = coronary artery bypass grafting; LDH = lactate dehydrogenase; PF = pleural fluid; PFA = pleural fluid analysis.
[a]Solid malignancy results in lymphocyte count between 50% and 70%.
[b]Dasatinib-induced pleural effusion.
[c]Only 2 transudates with low pH.
[d]Rheumatoid arthritis and empyema typically are the only effusions associated with glucose of < 5 mg/dL.

components (Table 5, criteria 2 and 3), and requiring simultaneous serum studies. Several alternative methods to distinguish transudative from exudative pleural effusions have been proposed. Heffner and colleagues[25] have suggested that the Light criteria be modified by decreasing the cutoff level of PF to serum LDH to 0.45. This modification has not been adopted in clinical practice because it violates the aforementioned principle of maintaining criteria that are highly sensitive in identifying exudates, but at the expense of lowering specificity.[26] Others have explored using an abbreviated version of the Light criteria by omitting criterion 2 (Table 5), which did not change the diagnostic accuracy of the Light criteria.[22] Several investigators have examined the diagnostic accuracy of a single PF test such as protein or LDH levels to distinguish transudative from exudative pleural effusions; however, these approaches have low accuracy.[22,27] A combination of 3 PF measurements (protein, cholesterol, and LDH) performed similarly to the Light criteria without serum testing (Table 5).[22,27,28] Another approach attempted to integrate clinical judgment by using Bayesian analysis, which combines the clinician's pretest probability with likelihood ratios derived from Light criteria components to calculate the posttest probability of an exudate.[29] However, this method has not gained widespread adoption because of its complexity. Despite multiple attempts at modifications and refinement over the past 6 decades, alternative approaches have not demonstrated superior diagnostic accuracy to the Light original criteria. Therefore, despite its drawbacks, the Light criteria remain the standard initial approach to PF classification.[22]

Transudative Pleural Effusions

A transudative pleural effusion can develop by several mechanisms: (1) increased hydrostatic pressure in pulmonary capillaries, leading to ultrafiltration across pleural membranes; (2) decreased systemic oncotic pressure; (3) decreased pleural pressure (trapped lung physiologic features); (4) movement or introduction of extravascular fluid into the pleural space (vide infra); or (5) a combination of these factors. The number of causes of transudative pleural effusions is limited (Table 6). The most common causes of transudative effusions are CHF and cirrhosis.[30]

TABLE 2] Special PF Testing Based on Suspected Disease

Suspected Diagnosis	Test	Values Suggestive of the Diagnosis
Chylothorax	Triglyceride	> 110 mg/dL
	Chylomicrons	50-110 mg/dL plus presence of chylomicron
Pseudochylothorax	Cholesterol	Cholesterol > 250 mg/dL
Hemothorax	Hematocrit	PF/B > 0.5
Esophageal rupture	Amylase (salivary isoenzyme)	200-2000 IU/L
Acute pancreatitis	Amylase	200-2000 IU/L
Pancreatico-pleural fistula/chronic pancreatitis	Amylase	> 100,000 IU/L
Tuberculous pleural effusion	Adenosine deaminase	> 40 U/L
Urinothorax	Creatinine	PF/S > 1
Bilothorax	Bilirubin	PF/S > 1
Duropleural fistula/ ventriculopleural shunt	β-2 transferrin	Presence of transferrin
Glycinothorax	Glycine	PF/S > 1
Lymphoma or multiple myeloma	Flowcytometry	Abnormal clonal lymphocytes

PF = pleural fluidPF = pleural fluid; PF/B = pleural fluid to blood ratio; PF/S = pleural fluid to serum ratio.

TABLE 3] Differential Causes of Pleural Effusion Based on Gross Inspection (Visual and Odor) of PF

Finding	Associated Conditions
Gross inspection (visual and odor)	
Bloody effusion	Hemothorax
	Malignancy
	Benign asbestos pleural effusion
	Post-cardiotomy injury syndrome
	Pulmonary infarction and trauma
	Kaposi sarcoma
Milky white	Chylothorax (can also appear as turbid serous)
	Pseudochylothorax
	Empyema (clear supernatant after centrifuge)
Green pleural effusion	Rheumatoid pleural effusion
	Bilothorax
	Malignant pleural effusion
Gross pus	Empyema
Food particles	Esophageal rupture
Black pleural effusion	*Rhizopus*
	Aspergillus
	Melanoma
Anchovy paste	Amebic liver abscess ruptured into pleural space
Putrid smell	Anaerobic empyema
Smell of urine	Urinothorax

PF = pleural fluid.

Transudates typically have low PF nucleated cell counts (< 500 cells/μL), low protein (< 3 g/dL), low cholesterol (< 45 mg/dL), and a slightly alkaline pH range than serum (range, 7.40-7.55).[31] The hallmark of a transudative pleural effusion of extravascular origin (vide infra) is a markedly low PF protein (< 1 g/dL).

The evaluation of a transudate should include a comprehensive cardiac assessment, including both left and right ventricular function, diastolic and systolic function, valvular heart disease, and pericardial conditions. Heart failure with preserved ejection and constrictive pericarditis often go unrecognized as underlying causes of pleural effusions. Hepatic hydrothorax may pose diagnostic challenges because ascites may not be apparent on conventional imaging.[32] This is the result of ascitic fluid migration into the pleural space through diaphragmatic fenestrations because of the pressure gradient between the pleural space and abdominal cavity, with the pressure in the former being more negative. Hints to the diagnosis of hepatic hydrothorax in these cases include a previous history of cirrhosis, ultrasonographic findings suggestive of cirrhosis, or subtle ascitic fluid present in perihepatic, perisplenic, and paracolic regions.

Exudative Pleural Effusions

An exudative pleural effusion develops through several mechanisms: (1) increased capillary permeability from infection or noninfectious pleural inflammation, (2) lymphatic blockage, (3) transdiaphragmatic migration of inflammatory or malignant peritoneal fluid, or (4) PF of extravascular origin. Infection and malignancy represent the 2 most common causes of exudative effusions.[30]

Although PFA findings associated with exudative pleural effusions demonstrate high specificity, they often have low sensitivity. PF cultures show positive results in only about 20% of pleural infections,[33] with AFB detected in 10% to 30% of TB pleural effusions.[8] Similarly, cytologic analysis identifies malignant cells in only 60% of malignant pleural effusions.[30] These limitations stresses the importance of interpreting PFA results within the context of the clinical pretest probability of the suspected disease. Despite these limitations, PFA remains a useful test for determining the cause of an exudative pleural effusion. Even when the PFA does not render a specific diagnosis, it can assist in narrowing the differential diagnosis (Table 7).

Nuances of the Light Criteria for Pleural Effusions

Although the Light criteria can provide general diagnostic guidance, several limitations and nuances should be considered.

Misclassification of Transudates as Exudates

The Light criteria are highly sensitive but modestly specific for the identification of exudates, and therefore can misclassify 25% to 30% of transudates as exudates (so-called pseudoexudates).[34] Transudates are misclassified as exudates most commonly in the following conditions: diuretics use, which increases PF protein concentration by the water absorption[35,36]; traumatic thoracenteses, which elevate pleural LDH levels from the hemolysis of blood[37]; and after coronary artery bypass grafting, which elevates PF protein by impairing lymphatic clearance.[38] In patients with a high clinical suspicion for CHF or hepatic hydrothorax,

TABLE 4] Definitive Diagnosis by PFA

Diagnosis	PF Characteristics	Clinical Characteristics
Transudates		
Urinothorax	PF/S creatinine > 1	Pleural effusion ipsilateral to the obstructive uropathy or genitourinary lesion
PD associated	PF/S glucose >> 1	PD with pleural effusion
Glycinothorax	PF/S glycine > 300	Pleural effusion after transurethral bladder surgery
Extravascular migration of central line	PF protein < 1 g/dL	Ipsilateral pleural effusion after newly placed CVC
	PF reflective of infusate fluid	
Duropleural fistula/migrate VP shunt	β-2-transferrin	Pleural effusion with ventriculoperitoneal shunt, spinal cord tumors, or spinal surgery
Exudates		
Chylothorax	Triglycerides > 110 mg/dL or triglycerides > 50 mg/dL plus chylomicron	Pleural effusion after trauma, cardiothoracic surgery, or lymphoma
Hemothorax	PF/B hematocrit > 0.5	Pleural effusion after trauma or cardiothoracic surgery
Pancreatico-pleural fistula	PF amylase > 100,000 U/L	Chronic pancreatitis with pseudocyst
Malignant pleural effusion	Positive cytologic findings	Metastatic cancer or ipsilateral lung cancer
Empyema	Pus	Pleural effusion ipsilateral to pneumonia
Bilothorax	PF/S bilirubin > 1	Right-sided pleural effusion with biliary pathologic features or surgery
Cholesterol effusion	PF cholesterol > 250 mg/dL	Chronic pleural effusion after TB or rheumatoid arthritis
Esophageal perforation	PF/S amylase > 1	Left-sided hydropneumothorax after esophageal procedure or pathologic features
	Food particles in PF	
Rheumatoid pleural effusion	Tad pole cell	Known or suspected RA, positive serologic findings for RA
	Pleural pH < 7.2	
	Glucose < 40 mg/dL	
	LDH > 1,000 IU/L	
Lupus pleuritis	LE cells	Known or suspected SLE, positive serologic findings for SLE
	Pleural pH < 7.30	

CVC = central venous catheter; LDH = lactate dehydrogenase; LE = lupus erythematosus; PD = peritoneal dialysis; PF = pleural fluid; PFA = pleural fluid analysis; PF/B = pleural fluid to blood ratio; PF/S = pleural fluid to serum ratio; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

serum to PF albumin gradient (> 1.2 g/dL) or PF to serum albumin ratio of < 0.6, respectively, can reclassify 80% of these effusions correctly as true transudates.[36] Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) also can be helpful in identifying CHF as a cause of a misclassified exudate. Serum NT-proBNP of > 1,500 μg/mL is highly suggestive of CHF in patients with pleural effuson.[39] Because PF and serum NT-proBNP levels are correlated closely, PF NT-proBNP level has limited additional value in distinguishing transudative from exudative pleural effusions.[40] A clinical scoring system of 5 parameters—age 75 years or older (3 points), serum to PF albumin gradient of > 1.2 g/dL (3 points), PF LDH of < 250 U/L (2 points), bilateral pleural effusion (2 points), and serum to PF protein gradient of > 2.5 g/dL (1 point)—has been validated for the identification of an effusion resulting from CHF that has been misclassified as an exudate by the Light criteria.[41] A score of ≥ 7 points has been shown to have a diagnostic accuracy of 92%, with a positive likelihood ratio of 12.7 and a negative likelihood ratio of 0.39, for correctly identifying transudates that have been misclassified as exudates by the Light criteria.

TABLE 5] Criteria to Differentiate Exudates From Transudates

Criteria	Values
Light criteria[a]	PF/S protein ≥ 0.5
	PF/S LDH > 0.6
	PF/ULNS LDH > 2/3
Modified Light criteria[a]	PF/S protein ≥ 0.5
	PF/S LDH > 0.45
	PF/ULNS LDH > 2/3
PF 3-test combination[a]	PF protein > 3 g/dL
	PF cholesterol > 55 mg/dL
	PF/ULNS LDH > 2/3

LDH = lactate dehydrogenase; PF = pleural fluid; PF/S = pleural fluid to serum ratio; ULNS = upper limit of normal serum value.
[a]Meeting any 1 criterion classifies effusion as exudate.

Protein-Discordant Exudate

A protein-discordant exudate is characterized by the presence of high PF protein concentration with normal PF LDH levels. These effusions are seen commonly in patients who have a transudative cause of pleural effusion and are being treated with diuretics or have conditions associated with a lesser degree of pleural inflammation or cellular turnover compared with capillary leak and endothelial disruption. Conditions that commonly cause protein-discordant exudates are shown in Table 1.[42]

TABLE 6] Common Causes of Transudates and Exudates

Transudates	Exudates
Congestive heart failure	Pneumonia
Mitral valve diseases	Malignancy
Hepatic hydrothorax	TB
Constrictive pericarditis	Post-cardiotomy syndrome
Volume overload	Autoimmune diseases
Urinothorax	Pulmonary embolism
Extravascular migration of central lines	Uremic pleural effusion
Duropleural fistula	Trauma
Ventriculoperitoneal shunt	Acute and chronic pancreatitis
Glycinothorax	Esophageal perforation
Peritoneal dialysis	Drug induced
Hypoalbuminemia	Chylothorax
Trapped lung	Yellow nail syndrome
Nephrotic syndrome	Benign asbestos pleural effusion
Superior vena cava obstruction	Sarcoidosis
Hypothyroidism	Nonspecific pleuritis
Atelectasis	

LDH-Discordant Exudates

LDH-discordant exudates are defined as a pleural effusions with a high PF LDH concentration and a normal PF protein level. Such effusions may be observed in patients with pneumonia or malignancy (Table 1).[42] The exact cause of LDH discordance is not well understood. It may be the result of a higher degree of pleural inflammation with minimal capillary endothelial disruption compared with concordant exudates, in which both PF LDH and protein are elevated.

Multiple Concurrent Causes

Multiple causes are responsible for up to 30% of pleural effusions.[43] The combination of CHF and pleural infection is the most frequent etiology of effusions from multiple causes. Generally, when both transudative and exudative mechanisms are present, the Light criteria usually classify these pleural effusions as transudates because hydrostatic pressure from the transudative process typically generates more fluid than the effects of increased capillary permeability and lymphatic blockage resulting from an exudative process.

Some disease states can cause either a transudative or exudative pleural effusion, which may present as a diagnostic challenge. Urinothorax usually is transudative, but it can be exudative when complicated by urinary infection.[44,45] Chylothorax typically is exudative, but it can be transudative in cases of cirrhosis or superior vena cava syndrome.[46,47]

PF of Extravascular Origin

PF of extravascular origin (PEEVO) is defined as a group of rare pleural effusions that do not originate from the pleural vasculature.[48] These effusions present a diagnostic challenge. PEEVO often are problematic to manage because they often recur. Pleural drainage of PEEVO usually is of transient benefit because a specific procedural intervention to address the underlying cause usually is required for their resolution. PEEVO can be transudative or exudative. Common causes of transudative PEEVO include hepatic hydrothorax, urinothorax, peritoneal dialysis-related effusions, extravascular migration of central lines, dural pleural fistulas, and ventricular-pleural or peritoneal shunts.

TABLE 7] Highly Suggestive Diagnosis by PFA

Diagnosis	PF Characteristics	Clinical Characteristics
Tuberculous pleural effusion	High protein > 5 g/dL	Unilateral pleural effusion in suspected TB (endemic area or exposure to TB)
	Lymphocyte > 80%	
	Mesothelial cells < 5%	
	ADA > 40 IU/L	
Complicated parapneumonic effusion	Nucleated cells > 50,000/μL	Pleural effusion ipsilateral to pneumonia
	Pleural pH < 7.2	
	Glucose < 60 mg/dL	
	LDH > 1,000 IU/L	
Sarcoidosis-associated pleural effusion	High protein > 4.5 g/dL	Known or suspected sarcoidosis
	Lymphocyte > 80%	
	Mildly elevated LDH	
Spontaneous bacterial pleuritis	ANC > 500/μL	Chronic liver disease with ascites
	ANC > 250/μL plus Gram stain	

ADA = adenosine deaminase; ANC = absolute neutrophil count; LDH = lactate dehydrogenase; PF = pleural fluid; PFA = pleural fluid analysis.

Other causes of exudative PEEVO include esophageal perforation, chylothorax, bilothorax, pancreatico-pleural fistulas, and enteral tube misplacement.

Case Example Continued

These PFA findings were not pathognomonic of a specific pleural disorder (Table 4). However, the finding of a lymphocytic-predominant (> 80% lymphocytes) exudative pleural effusion (pleural fluid to serum ratio protein, 0.71; pleural fluid to serum ratio LDH, 4.8) narrow the differential diagnosis (Table 1). When coupled with the clinical history, differential diagnoses are limited further to rheumatoid pleural effusion, tuberculous pleural effusion, sarcoidosis, and lymphoma. PF analysis findings of a sarcoidosis-associated pleural effusion are often indistinguishable from TB pleural effusion, with the exception of mildly elevated LDH seen in a sarcoidosis-associated pleural effusion.[49] Because of a high suspicion for TB, a thoracoscopic pleural biopsy was obtained that revealed necrotizing granuloma and nucleic acid amplification test showed positive results for *Mycobacterium tuberculosis* complex. The patient was treated with 4-drug regimen with complete resolution of the pleural effusion and symptoms. Knowledge of PF analysis (lymphocytic-predominant effusion) with high clinical suspicion based on the detailed travel history was helpful in reaching the diagnosis of pleural TB in a nonendemic area. Finally, a thoracoscopic pleural biopsy was helpful in securing the diagnosis of a tuberculous pleural effusion. A pleural biopsy specimen should be sent for mycobacterial cultures and drug sensitivity whenever TB is a diagnostic consideration. Pleural biopsy can be obtained by image-assisted needle biopsy or thoracoscopic pleural biopsy; both procedures have high and comparable diagnostic yields.[50]

Summary

PFA is essential for determining the cause of most pleural effusions. Although PFA is usually not diagnostic in isolation, often it can narrow the differential diagnosis of a pleural effusion and can be diagnostic when coupled with the patient's medical history and clinical presentation. Failure to analyze PF findings adequately may lead to misdiagnoses and unnecessary invasive procedures.

Future Directions

We believe that the diagnostic specificity of PFA is likely to improve exponentially. The emergence of multiomics and artificial intelligence with machine learning holds promise for identifying personalized biomarkers to improve the diagnosis and management of pleural disorders. PF biobanking may be helpful to accelerate the progress toward this goal.

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